CBER 2004: Innovation Advancing Public Health

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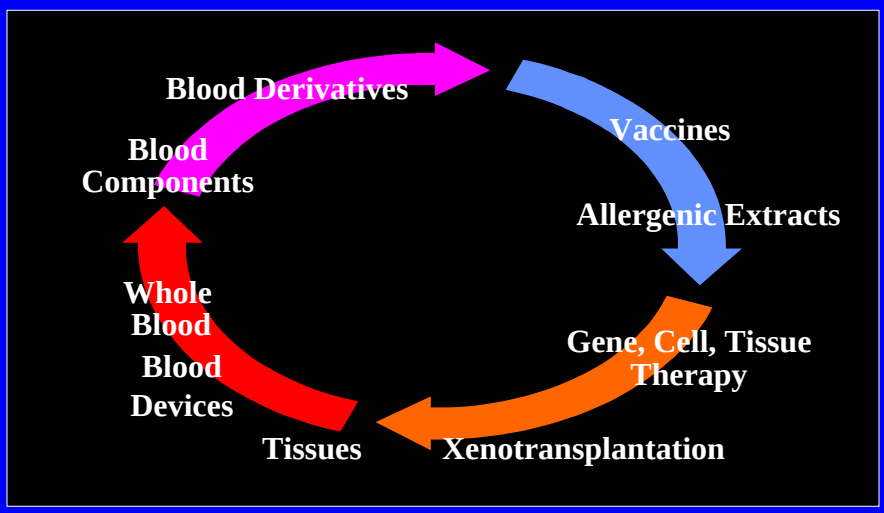
Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

- ***Protect and improve public and individual health in the US and, where feasible, globally***
- ***Facilitate the development, approval and access to safe and effective products and promising new technologies***
- ***Strengthen CBER as a preeminent regulatory organization for biologics***



Selected Accomplishments

- **Product Review/Approval:**
  - **CBER applications maintaining/increasing pace**
  - **Meeting all PDUFA & MDUFMA Milestones**
- **Public Health**
  - WNV Blood Donor Screening in 8 months
  - New HIV, hep C tests, TRANSNET Monitoring Pilot
  - Successful response to blood "white particles", SARS, other EID events: outreach on product development
    - **SARS examples; working with CDC/NIH in assuring provision of suitable vaccine isolates of SARS coronavirus; testing viral inactivation methods and parameters**
  - Risk Assessment/Guidances re: TSE, CT, blood safety
  - Other new products, e.g. tD, Flumist vaccines, fibrin sealant, α-1 proteinase

West Nile Update

- GenProbe and Roche NAT INDs
- ~ 6.4 million units tested in 2003!
  - Mostly as minipools (MP), targeted single donor NAT in highest incidence areas/periods
- ***>1000 WNV + donations intercepted and removed before transfusion***
  - Up to 20% of very low positive units may not be detected by mini-pooled (MP) NAT, few documented infections, studies in progress
- A major public health success achieved through proactive partnering, guidance and efforts of diagnostics & blood industries, CDC and FDA

Selected Accomplishments II.

- **Counterterrorism**
  - Now ~ 25% of CBER effort/resource use
  - Proactive needs/gap assessments/inventories
  - Emergency availability of critical countermeasures for smallpox, botulinum and anthrax threats (vaccines/blood/immunoglobulins)
  - Critical participation in multiple Task Forces for and outreach re: Product Development including industry, CDC, NIH and DOD
  - Proactive site visits/manufacturers' assistance
  - Implementation of Project BioShield
    - Technical assistance with requirements
    - Emergency Use Authorization

Selected Accomplishments III.

- **Patient Safety**
  - CMS and UHC Collaborations on vaccine/tissue safety
- **New Technologies**
  - Successful management of SCID/Gene Therapy events
  - BRMACs re: islet & cardiac cell transplantation
  - Cellular product CMCC review guidance, vaccine cell substrate guidance in final phases
  - Major research on GT and xeno safety, stem cell characterization, CT products and assays
- **International Efforts**
  - Re-designated WHO Collaborating Center
  - WHO Guideline on Pre-clinical Vaccine Studies
  - Xeno,Tissues and Gene Rx outreach with WHO, others
  - Plasma derivative, thrombin outreach and standards

Selected Accomplishments IV.

- **IT**
  - CBER Agency Leader in e submissions and secure digitally signed correspondence
  - 2003 Secretary's Award in e government
  - Gemcris: Secretary's Award (with NIH)
  - Under consolidated IT, Agency Lead for Gateway
- **Communications and Outreach:**
  - 2 million Web hits/month, 3 listservs
  - Rapid Dissemination of Critical Data: examples
    - **Outstanding responses to counterfeiting: e.g. Epogen/Procrit**
    - **Biologic Storage in Preparation for Hurricane Isabel**
    - **Alert on unlicensed flu vaccines/providers**

CBER 2004: New Initiatives

- **Efficient Risk Management**
  - **Enhanced Review Management and Processes**
    - ***Review Template Initiative***
      - ***Enhance consistency, quality of review and submissions as well as facilitating electronic processes***
    - **Review of Review Initiative**
      - ***Identify best practices/management and prepare for Agency-wide quality initiatives***
  - **GMPs for 21st Century**
    - **CBER serves on Steering Committee**
    - **CBER already had adopted many "new" practices endorsed**
      - **E.g.: scientists/clinicians on inspections, specialized teams and training, risk based prioritization, Center review of warning letters**
      - **Additional Center Initiative: enhance inspectional integration/coordination with product review process**

CBER 2004: Major Initiatives

- Patient Safety
  - Tissue Safety System
    - Finalization of Donor Suitability & Good Tissue Practice Rules
    - Creation of *Tissue Safety Team*
      - Interdisciplinary: OCTGT, OBE, OCBQ, OITM OCTMA
      - Active Surveillance as on ultimate goal
      - Adverse Event Reports and Analysis
      - Training, outreach, inspection and compliance

CBER 2004: Major New Initiatives

- Counterterrorism
  - CT Coordinating Committee
  - BioShield related guidance and evaluation
  - New technologies – delivery systems, vectors, transgenic Abs etc.
  - CT Product Safety Planning
    - Define measures to reduce potential vulnerabilities of CBER biologic products essential to the response to terrorist events

CBER 2004: Major Initiatives V

- *Strong FDA*
  - ***Reorganization/Refocusing of Director's and Management Offices***
  - ***Management Training Initiatives***
  - ***Risk Assessment, Management and Communication Training for Reviewers***
  - ***Global Strategic Plans***
    - Vaccine harmonization efforts and possible Global Vaccine Enhancement Program
- *Cross- Cutting Initiative:*

  Emerging Infectious Diseases
  - ***Products for prevention, treatment, diagnosis***
  - ***Protection of blood, cell, vaccine and tissue safety***

CBER: Major Approaches to Fostering Innovation

- Innovation through leadership & management
  - positive culture
  - problem solving, teamwork, partnerships
  - learning from successes and failures
  - efficiently used human and material resources
  - result-remove barriers, build bridges, improve efficiency
- Innovation in review and science
  - expert & science-based approaches to all processes e.g. review, risk management & communication
  - focus on helping new fields coalesce & move forward
    - Provide guidance and clarity
    - Identify problems; help bring about and make available needed solutions and tools e.g. "Critical Path"

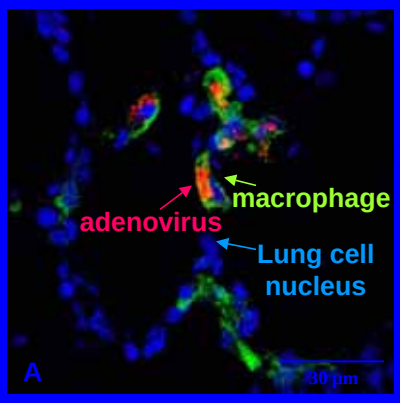
CBER Science & Critical Path Initiative

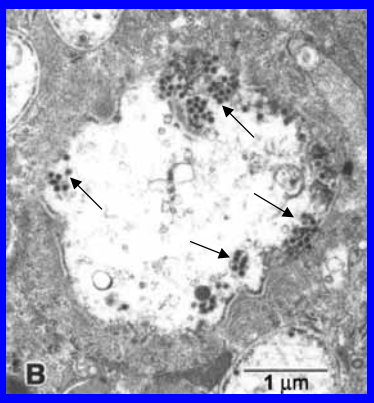
- *CBER Initiatives to track and focus research consistent with and supportive of FDA initiative*
- *Targeting unmet needs with regulatory implications to facilitate the development of products*
  - Benefits multiple sponsors; high impact for new fields, products w/ uncertain markets, public health
- Maintains staff "cutting edge" expertise needed for dealing with evolving biotechnologies
  - Scientific expertise and confidence foster objectivity
    - *Reduces risks of reflexive over- or under-protectiveness*
    - *Make regulation more scientific, less "defensive"*
- *Seeking increased outside participation and input*
  - Collaborations with multiple outside institutions
  - Plan to extend input & evaluation to broad programmatic areas & include identifying unmet needs and opportunities

Recent CBER Collaborative Science Supporting Innovation

- **Potency/effectiveness/standards**
  - **High throughput smallpox Ab/VIG potency assay**
  - **international Factor, thrombin, adenovirus standards**
  - **Proteomic monitoring of cancer treatment**
  - **surrogate markers/models of efficacy; TB, tularemia, hepC, pneumococcus, IGIV**
  - **embryonic stem cell gene expression**
- **Safety**
  - **West Nile testing standards and reagents**
  - **Vaccine/cell safety and adventitious agent tests (e.g. PERT, PERV, TSE)**
  - **Gene Rx , endothelial cell predictive toxicity models**
  - **Oxidative toxicity of RBC substitutes link to structure/chemistry**
- **Consistency/manufacturing/quality**
  - **conjugate vaccine synthesis methods**
  - **Prion inactivation and testing**
  - **Influenza seed strains, reassortants, stds & methods**

Adeno Vector-associated Lung Disease in Setting of Pre-existing Liver Disease

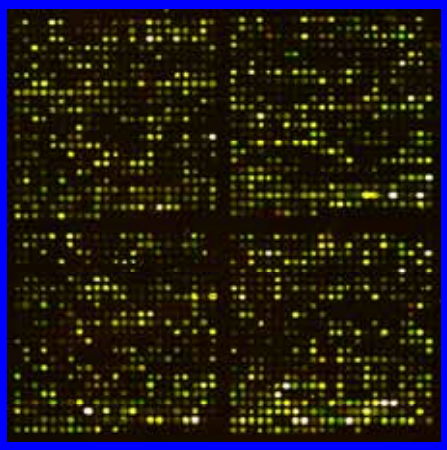


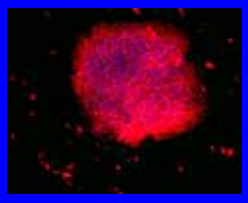


Adenovirus inside lung macrophages in rat with liver disease

Quality Assessment of Stem Cells by Gene Expression Profile Microarray

CBER/NIH collaboration finds 86 common "stemness" genes





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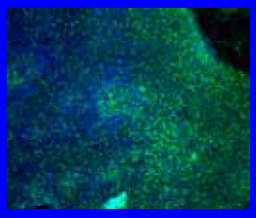

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Examples of Major Critical Path Investment Opportunities

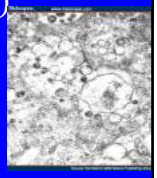
- New vaccine delivery systems/methods, rapid use vectors, adjuvants
- Develop/make available well characterized cell banks (and related methods to assay for safety/adventitious agents) useful for vaccine and other biologics production – and update guidance for use
- Characterization of cell therapies & links to standardized clinical/lab outcomes (e.g. HPSCs)
- Methods & validation of pathogen inactivation for blood, plasma, tissues and other products
- Multipathogen and rapid detection methodologies for biologics including blood and tissue products
- Improving longevity/storage of blood and tissues

Investing to Advance New Vaccine Technologies

- DNA vaccines & vectors:
  - distribution, integration
  - Safety, including tumorigenicity
- New vaccine platforms: Plug and play-ability to generalize and predict immunogenicity and safety
- Transgenics- relevant to multiple biologics
- Adjuvants, immune stimulants: develop data and confidence for safety and efficacy
  - CpG, lipid nanotech particles
  - mucosal/transdermal patch delivery
  - maternal vaccination

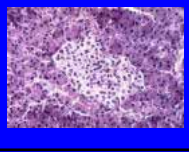
Investing to Develop & Facilitate Availability of Cell Substrates

- Vaccines, gene therapies, and recombinant proteins increasingly cell derived
- Cell based vaccines may offer enhanced flexibility and capacity for urgent production (e.g. influenza, smallpox)
- Increased number diversity of screened, well characterized cell banks needed “on the shelf”
  - Capable of performance (e.g. diverse virus types)
  - Tested for relevant infectious agents
  - Tested by well characterized and predictive tumorigenicity assays



Characterize Cellular Products and Link to Outcomes

- **Develop well characterized biomarkers predictive of product toxicity & efficacy**
  - Including *in vitro* expanded, selected and genetically modified cell lines
  - Identify meaningful changes in cell specifications or environmental "stress" on cells
- **Link molecular and immunologic data to standardized and measurable clinical outcomes across similar studies and products**
  - ***Markers and gene expression patterns of cell therapies that will predictably and reproducibly perform well as medical therapy***



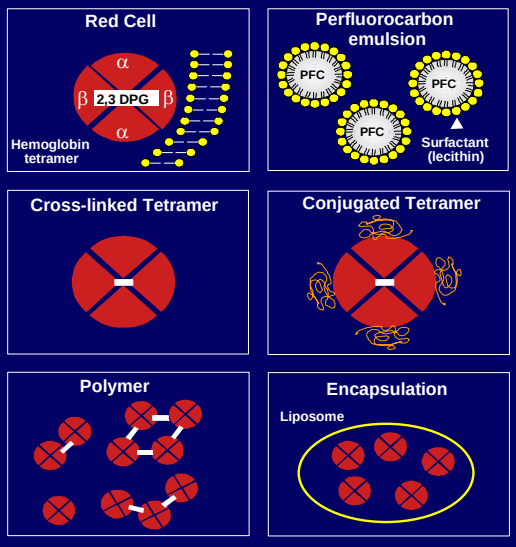
Detection & Inactivation of Emerging Pathogens in Blood, Cells, Tissue & Vaccine Products

- Multipathogen testing
  - Need to engage new, rapidly adaptable platforms
  - Nanotechnology and "flow through" assays
  - Bacterial contamination
- TSE rapid screening
- Blood and plasma products – methods to inactivate
  - In process determination of clearance of viruses & prions
  - New approaches to TSE's
  - Nanofiltration to reduce viral contamination
  - Chemical treatments
- Mechanisms for testing & decontamination of human tissues that preserve integrity

Better, Longer Lasting Blood, Cellular and Tissue Products

- Improved cryopreservation and thawing methods: development and validation (e.g. for RBC stockpiles, other cellular products)
- Improved hemopoeitic stem cell production, quality, and preservation
- Enhanced platelet preservation and quality
- Blood “substitutes” for field/urgent use

Various forms of Red Cell Substitutes



Thanks!

- ***We are proud of CBER, its staff & our mission and see a bright and promising future.***
- ***Together we can continue to enhance successful development of safe and effective products that benefit patients and promote public health***
- ***We seek your input and want to both work with you and know about your needs, strategies and ideas, as well.***

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